REMARKS

Claims 13-27 are pending in the instant application. The Applicants believe that any objections and rejections raised in the March 6, 2001 Office Action issued in parent application Serial No. 09/676,223 are addressed by the arguments made below.

I. The Amendments

The specification has been amended to correct typographical errors and to insert the address of the DSMZ. No matter is introduced by the amendments. A marked-up copy of the amendments to the specification is attached hereto as *Appendix A*.

Claims 1-12 have been canceled, without prejudice, and new Claims 13-27 have been added, for the purpose of more clearly defining what Applicants regard as the invention and for placing the rejected claims in condition for allowance. The new claims do not introduce new matter, and they are fully supported by the specification of the present application and the claims as originally filed. Specifically, new Claims 13, 15, 20, 22, 24, and 26 are supported by Claims 1-12 as originally filed and by the specification, for example at pages 2-4. New Claims 14, 16-19, 21, 23, 25, and 27 are supported by Claims 1-12 as originally filed. Therefore, entry of new Claims 13-27 under 37 C.F.R. §1.111 is respectfully requested.

The claims as amended are attached hereto as *Appendix B*. The claims as pending are attached hereto as *Appendix C*.

II. The Rejections

A. The Rejection Of Claims 1-12 Under 35 U.S.C. § 112

1. The Rejections Of Claims 1-12 Under 35 U.S.C. § 112, First Paragraph Are Obviated And/Or Overcome By The Zur Hausen Declaration

Claims 1-12 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and lack of written description. Both rejections are obviated and/or overcome by the enclosed zur Hausen Declaration confirming the deposit of the specific plasmid DNA sequences required to practice the invention, and its unrestricted availability. *See Exhibit 1.*

The Applicants believe that the zur Hausen Declaration overcome the rejection, and request that it be withdrawn.

2. The Rejections Of Claims 1-4, And 6 Under 35 U.S.C. § 112, Second Paragraph Are Obviated And/Or Overcome By The Amendments To The Claims

Claims 1-4, and 6 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These rejections are obviated and/or overcome by the amendments to the claims, and therefore, they should be withdrawn.

B. The Rejection Of Claims 5-9 Under 35 U.S.C. § 102

1. The Rejection Of Claims 5-9 Under U.S.C. § 102(e) Over Colosi Should Be Withdrawn In View Of Applicants' Arguments

Claims 5-9 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,004,797 ("Colosi"). This rejection is respectfully traversed.

Rejected Claims 5-9 correspond to new claims 20, 21, 24, and 25. New Claims 20, 21, 24, and 25 are directed to a method for producing an rAAV viral particle preparation which is not contaminated with helper viruses. The method involves the exposing of cells to a nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, where the ***nucleic acid comprises the complete AAV 5 sequence with exception of the E1 region***.

Colosi teaches, according to the Examiner's characterization, a method of producing AAV viral particles without using a helper virus; the non-AAV helper virus accessory functions, needed for AAV particle release, are derived from adenovirus, herpes virus and vaccinia virus. *See*, Office Action, at page 6-7. Colosi, however, does not teach the use of AAV helper virus sequences ***comprising the complete AAV 5 sequence with exception of the E1 region*** for developing AAV viral particles, as the presently claimed invention. Therefore, Colosi cannot anticipate the present claims.

In view of the above, the rejection of Claims 5-9 over Colosi should be withdrawn.

2. The Rejection Of Claims 5, 6, 8, And 9 Under U.S.C. § 102(e) Over Wang Should Be Withdrawn In View Of Applicants' Arguments

Claims 5, 6, 8, and 9 have been rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,872,005 ("Wang"). This rejection is respectfully traversed.

Rejected Claims 5, 6, 8, and 9 correspond to new claims 20, 21, 24, and 25. New Claims 20, 21, 24, and 25 are directed to a method for producing an rAAV viral particle preparation which is not contaminated with helper viruses. The method involves the exposing of cells to a nucleic acid comprising an AAV helper virus sequence developing

AAV viral particles, where the ***nucleic acid comprises the complete AAV 5 sequence with exception of the E1 region***.

Wang teaches, according to the Examiner's characterization, a method of producing helper virus free AAV viral particles using a cell line that contains the non-AAV complementing sequences necessary for AAV packaging. However, the presently claimed invention teaches the use of AAV helper virus sequences ***comprising the complete AAV 5 sequence with exception of the E1 region*** for developing AAV viral particles. Thus, Wang cannot anticipate the present claims.

In view of the above, the rejection of Claims 5, 6, 8, and 9 over Wang should be withdrawn.

C. The Rejection Of Claims 1-12 Under 35 U.S.C. § 103(a) Should Be Withdrawn In View Of Applicants' Arguments

Claims 1-12 have been rejected under 35 U.S.C. § 103(a) as being obvious over Colosi. This rejection is respectfully traversed.

Rejected Claims 1-12 correspond to new Claims 13-27. New Claims 13-27 are directed to a nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, where the nucleic acid comprises the complete AAV 5 sequence with exception of the E1 region, and further to compositions comprising such nucleic acid, and to methods using the same for the generation of AAV viral particles.

Colosi is, according to the Examiner's interpretation, directed to a method of producing a recombinant AAV viral particle that does not require helper virus; according to the Examiner, Colosi teaches that accessory functions necessary to support the rAAV particle production may be derived from adenovirus or herpes virus. Colosi teaches the construction

of a plasmid containing the VA RNA, E4 and E2a regions, however, as acknowledged by the Examiner, Colosi does not teach or suggest using a complete adenovirus genome with a deletion in the E1, or the E1 and L1 genes, as presently claimed.

The Examiner asserts that it would have been obvious to one of ordinary skill in the art to use a replication defective adenoviral genome to supply the necessary accessory genes for the AAV particle production. However, the Examiner fails to provide any support for this assertion. In particular, the Examiner does not show where there is a suggestion in the prior art to use an AAV helper virus sequence comprising the complete AAV 5 sequence with exception of the E1 region, or the L1 and E1 regions, respectively, for the production of AAV particles. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness, and the rejection of Claims 1-12 under 35 U.S.C. § 103(a) over Colosi must be withdrawn.

CONCLUSION

In view of the above remarks, the subject application is believed to be in good and proper order for allowance. Early notification to this effect is earnestly solicited.

If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 493-4935. The commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 16-1150 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date 30 October 2001

43,341

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Enclosures

APPENDIX A
Marked-up Paragraphs of Amended Specification

Please amend the specification as follows:

On page 1, line 11, please make the following amendment:

The present invention relates to [AA V DNA] AAV DNA having helper virus sequences, a system containing such a DNA and its use.

On page 3, lines 21-22, please make the following amendment:

An AAV DNA according to the invention can be prepared by common methods. By way of supplement, reference is made to Sambrook, J. et al., Molecular Cloning, A Laboratory Handbook (Vols. 1-3), Cold spring Habour, New York, (1989). Furthermore, reference is made, in Example 1, to the preparation of the pTG9585 AAV DNA according to the invention. This AAV DNA comprises the complete adenovirus 5 sequence with the exception of the E1 region, as helper virus sequences. PTG9585 is preferred. It was deposited with the [DSM [German-type collection of micr-organisms and cell cultures], Braunschweig] DSMZ - Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH, Mascheroderweg 1b, D-38124 Braunscheig, Germany, as plasmid pTG9585 under number [DSM] DSMZ 11248 on October 18, 1996. Also, an AAV DNA according to the invention is preferred which differs from pTG 9585 in that it has a deletion in the structural gene L1 of the adenovirus 5 sequence, particularly in the region of nucleotides 16614-18669. This AAV DNA is referred to as pTG9585 Δ 16614-18669. Besides, an AAV DNA according to the invention is preferred which differs from pTG 9585 in that it comprises two deletions from a total of 18323 base pairs, one deletion relating to great portions of the adenovirus capsid genes and the other deletion relating to the E3 region of adenovirus. This AAV DNA is referred to as pDG and was deposited with the [DSM] DSMZ as plasmid pDG under number [DSM] DSMZ 11817 on October 15, 1997.

On page 4, line 13, please make the following amendment:

rAAV viral particle preparations according to the invention are perfectly suited for the transduction of cells. It may be favorable for the preparations to be treated with [a Dnase] DNase prior to their use, so that free AAV DNA is degraded. The cells in consideration are

any cells which are present in a body or isolated from a body. Hence it is possible by the present invention to take measures for an *ex vivo* and *in vivo* gene therapy.

On page 5, line 7 and line 13, please make the following amendments:

The cloning strategy for obtaining pTG9585 is shown in fig. 1. An MMTV LTR fragment from PUC8MMTV (Fasel *et al.*, 1982, *EMBO J.* 1:3-7) is inserted in the multiple cloning site of plasmid pBSSKII(+) (company of Stratagene). Then, 4235 pb of AAV2 sequence from pAV2 Laughlin *et al.*, (1983, *Gene* 2:65-73) are inserted in this plasmid by means of a synthetic oligonucleotide adapter, which contain the complete rep gene and cap gene as well as the AAV2 promoters p19 and p40. Thus, the AAV2 promoter p5, which controls the expression of the Rep78 proteins and Rep68 proteins, respectively, is replaced in the resulting plasmid pBMA2 by the MMTV promoter. The complete expression cassette consisting of the MMTV-LTR and the AAV2 rep gene and cap gene is then inserted in the vector pAdRSVßgal in the place of the RSV-ßgal fragment [(J. Clin Invest. 90, 625-6300] Stratford Perricaudet *et al.*, 1992, *J. Clin. Invest.* 90 625-6300. The MMTV-AAV2 fragment is flanked in the thus resulting plasmid pAMA2 on both sides by adenoviral sequences (5': 0-1.0 map units; 3':9.4-18 map units).

APPENDIX B

Marked-Up Versions of Amended Claims

(Additions are underlined; Deletions are bracketed)

Please cancel Claims 1-12.

Please add the following new Claims 13-27:

13. (New) A nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, wherein said nucleic acid comprises the complete AAV 5 sequence with exception of the E1 region.

14. (New) The nucleic acid of Claim 13, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSMZ 11248.

15. (New) A nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, wherein said nucleic acid comprises the complete AAV 5 sequence with exception of the L1 and E1 region.

16. (New) The nucleic acid of Claim 15, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSMZ 11817.

17. (New) A composition comprising the nucleic acid of Claim 1, 2, 3, or 4, and an rAAV vector.

18. (New) The composition of Claim 17, further comprising a cell.

19. (New) The composition of Claim 18, wherein said cell is a mammalian cell.

20. (New) A method for producing an rAAV viral particle preparation which is not contaminated with helper viruses, comprising:

(a) exposing cells to a nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, wherein said nucleic acid comprises the complete AAV 5 sequence with exception of the E1 region;

(b) inducing said cells to develop rAAV viral particles; and

(c) isolating said rAAV viral particles.

21. (New) The method of Claim 20, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSM 11248.

22. (New) A method for producing an rAAV viral particle preparation which is not contaminated with helper viruses, comprising:

(a) exposing cells to a nucleic acid comprising an AAV helper virus sequence developing AAV viral particles, wherein said nucleic acid comprises the complete AAV 5 sequence with exception of the L1 and the E1 region;

(b) inducing said cells to develop rAAV viral particles; and

(c) isolating said rAAV viral particles.

23. (New) The method of Claim 22, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSMZ 11817.

24. (New) A method for producing an rAAV viral particle preparation which is not contaminated with helper viruses, comprising:

(a) exposing cells to a composition comprising (1) an AAV helper virus nucleic acid sequence developing AAV viral particles, wherein said nucleic acid sequence comprises the complete AAV 5 sequence with exception of the E1 region, and (2) an rAAV vector;

(b) inducing said cells to develop rAAV viral particles; and

(c) isolating said rAAV viral particles.

25. (New) The method of Claim 24, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSMZ 11248.

26. (New) A method for producing an rAAV viral particle preparation which is not contaminated with helper viruses, comprising:

(a) exposing cells to a composition comprising (1) an AAV helper virus nucleic acid sequence developing AAV viral particles, wherein said nucleic acid sequence comprises the complete AAV 5 sequence with exception of the L1 and the E1 region;

(b) inducing said cells to develop rAAV viral particles; and

(c) isolating said rAAV viral particles.

27. (New) The method of Claim 26, wherein said nucleic acid has been deposited with the Deutsche Sammlung von Mikroorganismen und Zellkulturen under DSMZ 11817.